REMARKS

Claims 27-36, 39, and 42-45 are currently pending in this application. Claim 43 is withdrawn from consideration as being drawn to a non-elected invention. Claims 44 and 45 are objected to for being in improper form. Claims 27-36, 39, 42, 44, and 45 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claims 42 is rejected under 35 U.S.C. § 103(a) for obviousness. Claims 27-36, 39, 42-45 are rejected for obviousness-type double patenting over claims 1-11 of U.S. Patent No. 6,372,432. Finally, the specification is objected to for improper incorporation of patent and non-patent documents by reference. By this reply, Applicants cancel claims 28, 34-36, 39, 42-43, and 45, amend claims 27 and 29-33, add new claim 46, and address each of the objections and rejections. Applicants reserve the right to pursue cancelled subject matter in a divisional application.

Support for the Amendments

Support for the amendment to claim 27 is found in the specification at, e.g., page 1, lines 4-9, page 3, lines 1-4 and 24-28, page 4, line 7, through page 5, line 11, and page 6, lines 10-24. Support for the amendment to claims 33 and 46 is found in the specification at, e.g., page 3, lines 6-22. Claims 29-32 have been amended to place the claims in proper claim format. No new matter is added by the amendment.

Applicants note that although the term "given, predefined," as is recited in present claims 27, 33, and 46 with respect to the pathological condition, is not present in the specification, *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of 35 U.S.C. § 112. Instead, the specification need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question (see, e.g., *In re Edwards*, 568 F.2d

1349, 1351-52, 196 U.S.P.Q. (BNA) 465, 467 (CCPA 1978). Here, the specification clearly teaches that a nucleic acid library can be prepared which is "characteristic of a given pathology" (see, e.g., page 3, lines 1-4). Thus, the pathological condition to be detected is known (i.e., "given") by the skilled artisan prior to employing the methods of the invention, and the pathological condition is "predefined" based on the nucleic acid library which is characteristic of the pathological condition. Accordingly, the term "given, predefined" is reasonably derived from the specification and is not new matter.

Claim Objections

The Examiner objects to claims 44 and 45 because, as dependent claims, they are "separated from their respective independent claims by a plurality of other independent claims" (Office Action, p. 2). Applicants have canceled claims 44, and 45. This objection may now be withdrawn.

Objection to the Specification

The Examiner objects to the specification, stating:

> The specification is objected to as documents have been improperly incorporated by reference. It is noted with particularity that the instant disclosure makes reference to various foreign patent document[s], both published and unpublished, as well as non-patent publications which are in turn being relied upon for disclosing how the claimed invention is to be made and used. Office Action, p. 2.

The Examiner further states that the language used in the specification "fails to specify what specific information applicant seeks to incorporate by reference and just where the specific information is to be found in each of the cited documents" (Office Action, p. 3). The Examiner

also cites *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d at 1679 (Fed. Cir. 2000), which states in relevant part:

> To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.

Finally, the Examiner directs Applicants to M.P.E.P. § 608.01(p)(I)(A), which states:

> In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

Applicants respectfully disagree with the Examiner's objection to the specification. The patent and non-patent documents recited in the specification are merely provided as background references that can be consulted by the skilled artisan.

For example, the technique of subtractive hybridization, which is discussed on page 17, line 25, through page 19, line 7, has been known since at least 1981, as is evidenced by Vitek et al. (Nucl. Acids Res. 9:1191-1202, 1981; a copy of which is provided). As one embodiment of the invention, the specification discloses the subtractive hybridization method reported by Kohne et al. (Biochemistry, 16:5329-5341, 1977) and Miller and Riblet (Nucl. Acids Res. 23:2339-2340, 1995), which is referred to as phenol emulsion reassociation technique (PERT). This subtraction based genomic cloning method is but one possible method that can be used by the skilled artisan, as is made clear by the specification on page 18, lines 26-28, which states: "Any other hybridization method in liquid phase, preferably in emulsion, can be used within the scope of the present invention. Furthermore, the hybridization can also be done with one of the strands immobilized on a support." Thus, practicing the method of present claims 27, 29-33, 44, and 46 does not require performance of the methods of Kohne et al. and Miller and Riblet. Thus, these

references have been properly cited in the specification.

The reference in the specification to international patent application PCT/FR 99/00547, noted by the Examiner on page 2 of the Office Action, is also provided as background for the skilled artisan. PCT/FR 99/00547, which was published as WO 99/46403 on September 16, 1999, is cited in the present specification for its disclosure of methods, e.g., the "DATAS methodology," for the preparation of nucleic acid libraries for use in the method of present claims 27, 29-33, 44, and 46. Each of the methods disclosed in PCT/FR 99/00547 are disclosed in enabling detail in the present specification. For example, the specification teaches the DATAS methodology, stating:

> banks can be prepared by hybridization between the nucleic acid population derived from cells isolated from the blood in a pathological situation, and the nucleic acid population derived from circulating cells in the control situation, and isolation, from the hybrids formed, of the nucleic acids corresponding to differential splicing. (Page 17, lines 18-22.)

The specification also discloses several other methods, all of which are well known in the art, which can be used by the skilled artisan for preparing the nucleic acid molecules of the library, including, e.g., high flow sequencing electronic subtraction, serial analysis of gene expression (SAGE), nucleic acid arrays, differential display, and subtractive cloning (see page 12, line 15, through page 14, line 8). Thus, the techniques and methods disclosed in PCT/FR 99/00547 are adequately disclosed in the present specification, and the skilled artisan can easily practice the method of present claims 27, 29-33, 44, and 46 based on the present specification without the need to consult PCT/FR 99/00547. Thus, reference to PCT/FR 99/00547 in the specification is provided merely as background for the skilled artisan.

If the Examiner disagrees with Applicants' position, Applicants would be willing to

provide a Declaration stating that the methods and techniques disclosed by the cited references are either fully enabled by the teachings in the present specification or are so well known in the art that the skilled artisan would need no further disclosure in the specification pertaining to these references for the practice of the method of present claims 27, 29-33, 44, and 46. In any event, Applicants respectfully request that the Examiner's objection to the specification be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 27-36, 39, 42, 44, and 45 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states that "[t]he claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, p. 5). Applicants respectfully disagree, but have cancelled claims 28, 34-36, 39, 42-43, and 45. Thus, the rejection as it applies to these claims can now be withdrawn. Applicants have also amended claims 27 and 29-33, and added new claim 46 to more clearly recite the subject matter Applicants regard as their invention.

As presently amended, independent claim 27 recites an *in vitro* method for detecting the presence of a given, predefined pathological condition in a human subject. The method involves three steps: i) providing a sample of blood cells (comprising lymphocytes, macrophages, monocytes, or dendritic cells) from a subject (i.e., a test subject who is being tested for the presence of the given, predefined pathological condition), ii) preparing nucleic acid molecules from the sample, and iii) obtaining a hybridization profile by hybridizing all or part of the nucleic acid molecules prepared from the sample of blood cells obtained from the subject with at least one nucleic acid library. The nucleic acid library is prepared from differentially spliced

ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects having the given, predefined pathological condition, and the RNAs are specific for the pathological condition sought to be detected. Because the nucleic acid molecules of the library are markers for the pathological condition, hybridization between the nucleic acid library and nucleic acid molecules from a test subject indicates the presence of the given, predefined pathological condition in the test subject.

As noted in the previous Reply to Office Action:

> An advantage of Applicants' invention is that neither the sequences of the nucleic acid molecules of the test sample, *nor the sequences of the nucleic acid molecules of the reference sample (i.e., the "library") need to be known to practice the invention*. All that is required is that the skilled artisan be able to obtain the nucleic acid molecules of the test sample and reference samples and to hybridize the two samples. Neither procedure (i.e., the preparation of the nucleic acid molecules or their hybridization) requires anything more than routine skill in the art. (Page 15, Reply to Office Action, August 4, 2004).

This advantage is acknowledged by the Examiner in the present Office Action, which states that "agreement is reached in that one may not need to know the nucleotide sequence of the nucleic acids that comprise the test sample or the reference" (see page 14 of the Office Action). Thus, by the Examiner's own admission, these elements of Applicants' method satisfy the written description requirement. Because each step of Applicants' method can be performed without knowing the sequence of the test nucleic acid molecules or the nucleic molecules of the library, a written description of these sequences, beyond what is already provided by Applicants' specification, is unnecessary.

In addition, the Examiner raises the issue of whether the specification satisfies the written description requirement with respect to "how one [skilled in the art] is to draw any conclusion

when the pathological condition is not associated with any gene splicing event in any blood cell, but is the result of a condition found in non-blood cells" and "just what [hybridization] profiles are to be associated with which pathological condition(s) in any and all mammalians" (Office Action, p. 9). Applicants note that it is the direct or indirect contact of blood cells with the diseased cells or tissue in the subject, which may include blood or non-blood cells, that triggers the expression of differentially spliced RNAs characteristic of the pathological condition in the blood cells (see the specification at, e.g., page 4, line 25, through page 5, line 11). Thus, any pathological condition that promotes the expression of differentially spliced RNAs in a subject's blood cells can be detected using the method of present claims 27, 29-33, 44, and 46, regardless of whether the pathological condition is associated with blood cells or non-blood cells. Furthermore, because the nucleic acid library is prepared from differentially spliced ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects having the given, predefined pathological condition, as is discussed above, any hybridization between nucleic acid molecules of the test sample and the nucleic acid library indicates the presence of the pathological condition in the test subject. Thus, it is unnecessary for Applicants to describe the hybridization profiles because any hybridization indicates a positive result.

Finally, the Examiner states:

> The claimed methods...have been interpreted as encompassing virtually any pathological condition, as well as any degree of exposure to a pathological condition. Said "exposure" has been construed as encompassing, but not limited to, having the cells of an individual, e.g., a health care provider, coming into direct or indirect contact with an individual that has a pathological condition. Said "pathological condition" has also been construed as encompassing diseases of unknown etiology, as well as individual being in the same general environment (e.g., a room) where a pathological agent (virus, bacteria, fungi, amoeba, helminth, carcinogen, etc.) is also to be found wherein [s]aid pathological agent is capable of causing a disease. Said "pathological condition" has also been construed as

> encompass[ing] exposure to UV light normally associated with sunlight. Office Action, p. 8.

Applicants point out that claim 27, as presently amended, recites that the pathological condition is one that is given and predefined, meaning that the pathological condition sought to be detected in the human subject is one that is known by the skilled artisan. Thus, pending claims 27, 29-33, 44, and 46 no longer encompass diseases of unknown etiology. Furthermore, the method of claims 27, 29-33, 44, and 46 does not encompass "any degree of exposure to a pathological condition," as indicated by the Examiner. Rather, the method involves the detection of a pathological condition in a subject by determining whether the blood cells of the subject have come into direct or indirect contact with diseased cells or tissues within the body of the subject; the contacting does not occur outside of the body. Thus, Applicants believe that claims 27, 29-33, 44, and 46, as presently amended, address this issue raised by the Examiner.

For all of the reasons provided above, Applicants' specification clearly satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, by providing a thorough description of the claimed invention with all of its limitations such that one skilled in the art can reasonably conclude that Applicants were in possession of the claimed invention (see M.P.E.P. § 2163). Accordingly, Applicants respectfully request that the rejection of claims 27-36, 39, 42, 44, and 45 under 35 U.S.C. § 112, first paragraph, for lack of written description be withdrawn, and that the rejection should not be applied to new claim 46.

Rejections under 35 U.S.C. § 103(a)

Claim 42 is rejected under 35 U.S.C. § 103(a) "as being unpatentable over applicant's representative admissions in the response of 28 October 2004." Office Action, p. 18. The

Examiner states:

> Applicant's representative admits at page 17 that: "Applicants' invention is not the discovery of the nucleic acids [sic] molecules specific for the pathological condition per se, rather, it is the discovery of the...[use] of those nucleic acid molecule in detection methods...[and] the genus of nucleic acid molecules recited in present claims27-36, 38, and 42 for use as the 'library' would have been known to the skilled artisan at the time of filing the present application and obtaining these nucleic acid molecules would not have been new or unconventional in the art."
> In view of the foregoing admission by Applicant's representative as to what constitute [sic] the invention of applicant, claim 42 is rejected under 35 U.S.C. 103(a)... Office Action, p. 18

Applicants respectfully disagree that the above admission provides the basis for the rejection under 35 U.S.C. § 103(a) of a claim directed to a kit that includes a support having a plurality of nucleic acid molecules deposited thereon, in which the nucleic acid molecules are specific for differentially spliced gene products present in a mammalian blood cell exposed to or experiencing a pathological condition. In the interest of expediting prosecution of present claims 27, 29-33, 44, and 46, Applicants have cancelled claim 42. This rejection can now be withdrawn.

Obviousness-Type Double-Patenting Rejections

Claims 27-36, 39, and 42-45 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,372,432. Applicants will submit a terminal disclaimer, if necessary, to overcome this rejection once otherwise allowable subject matter has been determined.

CONCLUSION

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for one month, to and including July 21, 2005, and a check for the fee required under 37 C.F.R. § 1.17(a). Applicants note that a two month extension of time has already been obtained.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 19, 2005

Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045